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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
HIROTOSHI ISHIDA, ET AL. : EXAMINER: TRAN LIEN, THUY
SERIAL NO: 10/722,679 and 90/007,160 :
FILED: NOVEMBER 28, 2003 : GROUP ART UNIT: 1761
FOR: SWEETENER COMPOSITION :

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR 1.97

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

Pursuant to 37 C.F.R. §1.56 and 37 C.F.R. §1.97, Applicants wish to make of record the following information:

Applicants undertook testing to confirm if pure C-type crystal of N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine 1-methyl ester ("DMB-APM" or "neotame") is obtained by the conditions described in U.S. Patent No. 5,480,668, as described at col. 7, lines 24-51, or in U.S. Patent No. 5,728,862, as described at col. 4, lines 32-49.

Preparation of Test Samples

(1) Run 1: A methanol/water solvent according to U. S. Patent 5,728,862 (17-25% aqueous methanol solution) was prepared by mixing 30.05 g of methanol and 105.17 of water. Thereafter, 6.41 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 49.92 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals

were obtained when cooled down to 10°C. The cooling crystallization according to U.S. Patent 5,728,862 was carried out at 10-15°C for 2 to 12 hours. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(2) Run 2: An ethanol/water solvent according to U.S. Patent No. 5,480,668 was prepared by mixing 25 ml of ethanol and 25 ml of water. Thereafter, 11.06 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 30.05 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(3) Run 3: Acetonitrile was used as solvent according to U.S. Patent No. 5,480,668. 17.51 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.1 g of acetonitrile and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated

solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(4) Run 4: A methanol/water solvent according to U.S. Patent No. 5,728,862 (17-25% aqueous methanol solution) was prepared by mixing 30.05 g of methanol and 105.17 of water. Thereafter, 4.2 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.24 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(5) Run 5: An ethanol/water solvent according to U.S. Patent No. 5,480,668 was prepared by mixing 25 ml of ethanol and 25 ml of water. Thereafter, 9.84 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.06 g of the solvent and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

(6) Run 6: Acetonitrile was used as solvent according to U.S. Patent 5,480,668. 10.47 g of DMB-APM (NutraSweet Co.'s Neotame lot # D106023325) was added to 20.18 g of acetonitrile and dissolved completely by heating to 60°C. The amount of DMB-APM was determined according to the preliminary test to study the amounts in which crystals were obtained when cooled down to 10°C. The cooling crystallization was carried out at 10-15°C for 2 to 12 hours, as in U.S. Patent No. 5,728,862. The solution was cooled down from 60 to 10°C at a rate of 10°C per hour and then kept at 10°C for crystallization. The precipitated solid was filtered by suction filtration and dried by vacuum drier (Yamato Scientific Co's DP33) at 40°C for 16 hours. Crystalline sample was obtained.

Analyses

Water content of the dried sample was analyzed by Karl-Fischer moisture analyzer MKA-210 (Kyoto Electronics Manufacturing Co. Ltd) and crystal type was analyzed by X ray diffractometer (PANalytical's X'Pert with X'Celerator, Tube:Cu,30mA,40kV,Sampling width: 0.020°,scanning speed :3°/min, wave length:1.54056 Å, 2θ:4-30°).

Result

The results are shown in Table 1.

Table 1.

| | Solvent | US Patent | Amount of added neotame | Concentration of added neotame | Temp. of precipitation | Time of precipitation | Amount of crystal | Water content | Type of crystal |
|---------------|-----------------------|-----------|-------------------------|--------------------------------|------------------------|-----------------------|-------------------|---------------|-----------------|
| | | | (g) | (weight %) | (°C) | (hr:min) | (g) | (weight %) | |
| Added neotame | - | - | - | - | - | - | - | 5.812 | A |
| Run-1 | MeOH:H ₂ O | 5,728,862 | 6.41 | 11.38 | 18.90 | 4:12 | 4.72 | 0.4083 | G |
| Run-2 | EtOH:H ₂ O | 5,480,668 | 11.06 | 26.90 | 12.44 | 4:50 | 6.80 | 0.184 | G |
| Run-3 | MeCN | 5,480,668 | 17.51 | 46.56 | 16.78 | 4:25 | 16.51 | 0.1223 | A+C |
| Run-4 | MeOH:H ₂ O | 5,728,862 | 4.20 | 17.18 | 10.10 | 5:36 | 4.21 | 10.144 | A+F |
| Run-5 | EtOH:H ₂ O | 5,480,668 | 9.84 | 32.91 | 10.87 | 4:58 | 8.69 | 3.3418 | G |
| Run-6 | MeCN | 5,480,668 | 10.47 | 34.16 | 10.00 | 8:25 | 3.25 | 0.2451 | A+C |

Application No. 10/722,678 & 90/007,160
Information Disclosure Statement

Applicants respectfully request due consideration of this information.

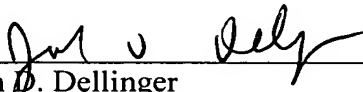
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